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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/775,554 | 02/09/2004 | Meng Yang | 312762004400 | 6701 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| ART UNIT | PAPER NUMBER |
| 1633 | |
| MAIL DATE | DELIVERY MODE |
| 12/07/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/775,554 | YANG ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/2/09 has been entered. Applicant's amendment filed 9/4/09, previously non-entered, and the amendment filed with the RCE have both been entered. Claims 19-20 have been canceled. Claims 1-3 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

***Election/Restrictions***

Applicant's claim amendment has canceled all claims drawn to the elected subject matter of Group I. The claims as amended now recite the subject matter of non-elected Group II, see the restriction requirement mailed on 8/8/06. In the response filed on 10/16/06, the applicant elected without traverse Group I. The examiner contacted applicant's representative on 12/2/09 to discuss the fact that no claims currently pending corresponded to the elected subject matter. A separate interview summary has been mailed to applicant. The applicant's representative indicated that they wished to switch inventions from Group I to Group II. The examiner agreed

to this switch. For the record, the restriction requirement still stands, but the subject matter now elected without traverse for examination corresponds to Group II.

***Claim Rejections - 35 USC § 103***

The rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over WO 02/28188 A1 (4/1/02), hereafter referred to as Kern, in view of Okabe et al. (1997) FEBS Lett., Vol. 467, 313-319 is withdrawn in view of applicant's amendments to the claims which now read on an immunocompromised transgenic rodent which expresses a first fluorescent protein in all tissues except hair and erythrocytes and which has been modified to contain a tumor that expresses a second fluorescent protein that emits a wavelength different from that of the first fluorescent protein.

Claims 1-3 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al. (1997) FEBS Lett., Vol. 467, 313-319, in view of WO 02/28188 A1 (4/1/02), hereafter referred to as Kern, and Yang et al. (2002) PNAS, Vol. 99(6), 3824-3829. It is noted that the authorship of Yang et al. and the inventorship of the instant application are not the same.

Okabe et al. teaches the production of a transgenic mouse comprising a transgene encoding GFP under control of the chicken beta-actin promoter (Okabe et al., page 313). Okabe et al. teaches that GFP was expressed in all tissues of the transgenic mouse with the exception of erythrocytes and hair (Okabe et al., page 313). Okabe et al. further teaches that the transgenic

mice expressing GFP can be used as a model of tumorigenesis by implanting non-green tumor cells into the 'green mice' (Okabe et al., page 319, column 2).

Okabe et al. differs from the instant invention by not teaching that the transgenic GFP mouse is immunodeficient, and that the non-green tumor expresses a second fluorescent protein which emits a wavelength different from GFP. Kern supplements Okabe et al. by teaching that transgenic immunodeficient organisms which exhibits a detectable trait such as the expression of a detectable marker can be used as a host for donor tumor xenografts (Kern, pages 4-6). More specifically, Kern teaches that the organism is a transgenic mouse which is the offspring of a nu/nu mouse and which expresses the detectable marker green fluorescent protein (Kern, page 4, and page 23, claims 18-24). Kern further teaches methods of making such as a mouse by stably integrating the detectable gene into the chromosome of a mouse embryonic stem cell and using the embryonic cell to develop strains of homozygous mice having two copies of the integrated construct in every cell, and then breeding the mice with nu/nu mice to produce mice that are homozygous for the transgene and homozygous for immunodeficiency (Kern, pages 10-11). Kern further teaches the constitutive expression of green fluorescent protein in the nu/nu mice (Kern, pages 13). Note in particular that Kern et al. teaches breeding the mouse transgenic for the selectable trait, such as constitutive GFP expression, to heterozygosity or homozygosity, where the transgene is integrated into the chromosomes of every cell in the mouse, and then cross-breeding that strain to a nu/nu mouse strain to create a homozygous GFP+/GFP+:nu/nu mouse or a heterozygous GFP+/-:nu/nu mouse (Kern, pages 10-11, bridging paragraph).

Yang et al. further supplements Okabe et al. by teaching that rat tumors cells transformed to express the gene for red fluorescent protein (RFP) can be transplanted into nude mice and are

easily detectable (Yang et al., pages 3825, and 3827-3828). Yang et al. further teaches that both GFP and RFP expressing cells in a nude mouse can be visualized at the same time using dual color imaging (Yang et al., pages 3827-3829).

Based on the specific motivation provided by Kern for breeding a transgenic mouse constitutively expressing GFP with an immunodeficient nu/nu mouse to produce a homozygous GFP+/GFP+:nu/nu mouse capable of growing a tumor xenograph, it would have been *prima facie* obvious to the skilled artisan at the time of filing to breed the GFP transgenic mouse of Okabe et al., where GFP is under transcriptional control of the constitutive beta-actin promoter, with a nu/nu mouse as taught by Kern to produce an immunodeficient transgenic mouse which expresses GFP in all tissues except hair and erythrocytes and which can host a donor tumor xenograft. Further, based on the well developed techniques of breeding mice at the time of filing, the specific guidance provided by Kern for breeding GFP transgenic mice with nu/nu mice and the detailed guidance provided by Okabe et al. for making a transgenic mouse encoding GFP under control of a beta-actin promoter, the skilled artisan would have had a reasonable expectation of success in making an immunodeficient GFP transgenic mouse. In addition, based on the motivation to implant a non-green tumor into GFP expressing transgenic mice provided by Okabe et al., and the teachings of Yang et al. that RFP expressing xenogenic tumors are readily detectable in nude mice and that dual-color imaging allows for the detection of both RFP and GFP expressing cells in the same mouse, it would have been *prima facie* obvious to the skilled artisan at the time of filing to implant an RFP expressing tumor xenograft into a GFP nude mouse with a reasonable expectation of success in both making the mouse as claimed and in visualizing both GFP and RFP expressing cells within the mouse.

Claims 1-3 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Okabe et al. (1997) FEBS Lett., Vol. 467, 313-319, in view of WO 02/28188 A1 (4/1/02), hereafter referred to as Kern, and Verkhusha et al. (2001) J. Biol. Chem., Vol. 276(32), 29621-29624.

Okabe et al. teaches the production of a transgenic mouse comprising a transgene encoding GFP under control of the chicken beta-actin promoter (Okabe et al., page 313). Okabe et al. teaches that GFP was expressed in all tissues of the transgenic mouse with the exception of erythrocytes and hair (Okabe et al., page 313). Okabe et al. further teaches that the transgenic mice expressing GFP can be used as a model of tumorigenesis by implanting non-green tumor cells into the 'green mice' (Okabe et al., page 319, column 2).

Okabe et al. differs from the instant invention by not teaching that the transgenic GFP mouse is immunodeficient, and that the non-green tumor expresses a second fluorescent protein which emits a wavelength different from GFP. Kern supplements Okabe et al. by teaching that transgenic immunodeficient organisms which exhibits a detectable trait such as the expression of a detectable marker can be used as a host for donor tumor xenografts (Kern, pages 4-6). More specifically, Kern teaches that the organism is a transgenic mouse which is the offspring of a nu/nu mouse and which expresses the detectable marker green fluorescent protein (Kern, page 4, and page 23, claims 18-24). Kern further teaches methods of making such as a mouse by stably integrating the detectable gene into the chromosome of a mouse embryonic stem cell and using the embryonic cell to develop strains of homozygous mice having two copies of the integrated construct in every cell, and then breeding the mice with nu/nu mice to produce mice that are homozygous for the transgene and homozygous for immunodeficiency (Kern, pages 10-11).

Kern further teaches the constitutive expression of green fluorescent protein in the nu/nu mice (Kern, pages 13). Note in particular that Kern et al. teaches breeding the mouse transgenic for the selectable trait, such as constitutive GFP expression, to heterozygosity or homozygosity, where the transgene is integrated into the chromosomes of every cell in the mouse, and then cross-breeding that strain to a nu/nu mouse strain to create a homozygous GFP+/GFP+:nu/nu mouse or a heterozygous GFP+/-:nu/nu mouse (Kern, pages 10-11, bridging paragraph).

Verkhusha et al. further supplements Okabe et al. by teaching a variant of RFP with increased fluorescence which can be used to label mammalian cells and which has improved properties for dual color imaging with GFP expressing cells (Verkhusha et al., pages 29621-29622).

Based on the specific motivation provided by Kern for breeding a transgenic mouse constitutively expressing GFP with an immunodeficient nu/nu mouse to produce a homozygous GFP+/GFP+:nu/nu mouse capable of growing a tumor xenograph, it would have been *prima facie* obvious to the skilled artisan at the time of filing to breed the GFP transgenic mouse of Okabe et al., where GFP is under transcriptional control of the constitutive beta-actin promoter, with a nu/nu mouse as taught by Kern to produce an immunodeficient transgenic mouse which expresses GFP in all tissues except hair and erythrocytes and which can host a donor tumor xenograft. Further, based on the well developed techniques of breeding mice at the time of filing, the specific guidance provided by Kern for breeding GFP transgenic mice with nu/nu mice and the detailed guidance provided by Okabe et al. for making a transgenic mouse encoding GFP under control of a beta-actin promoter, the skilled artisan would have had a reasonable expectation of success in making an immunodeficient GFP transgenic mouse. In addition, based

on the motivation to implant a non-green tumor into GFP expressing transgenic mice provided by Okabe et al., and the teachings of Verkhusha et al. that RFP expressing mammalian cells are readily detectable and that dual-color imaging allows for the detection of both RFP and GFP expressing cells in the same organism, it would have been *prima facie* obvious to the skilled artisan at the time of filing to implant an RFP expressing tumor xenograft into a GFP nude mouse with a reasonable expectation of success in both making the mouse and in visualizing both GFP and RFP expressing cells within the mouse.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, the technology center fax number is (571) 273-8300. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

*/Anne Marie S. Wehbé/*
Primary Examiner, A.U. 1633